News focus

Setback spurs Parkinson's disease research

Last month's report of no benefit from the transplantation of foetal cells into the brains of Parkinson's disease patients sent alarm bells ringing. But researchers believe that the field still holds promise as one of the best prospects for developing new treatments for this and other degenerative neuronal diseases, reports Nigel Williams

The media worldwide seized on the results of the first controlled trial of the technique of implanting foetal cells into the brains of Parkinson's disease patients, published last month, which found no overall benefit and left a number of the patients with tragic side effects which cannot be undone. But many researchers are concerned that the response to this new study, which some newspapers called a 'catastrophe', may overshadow a large body of promising and expanding work and are keen to flag up cell transplantation as one of the best chances of new treatments for this and other neurodegenerative diseases.

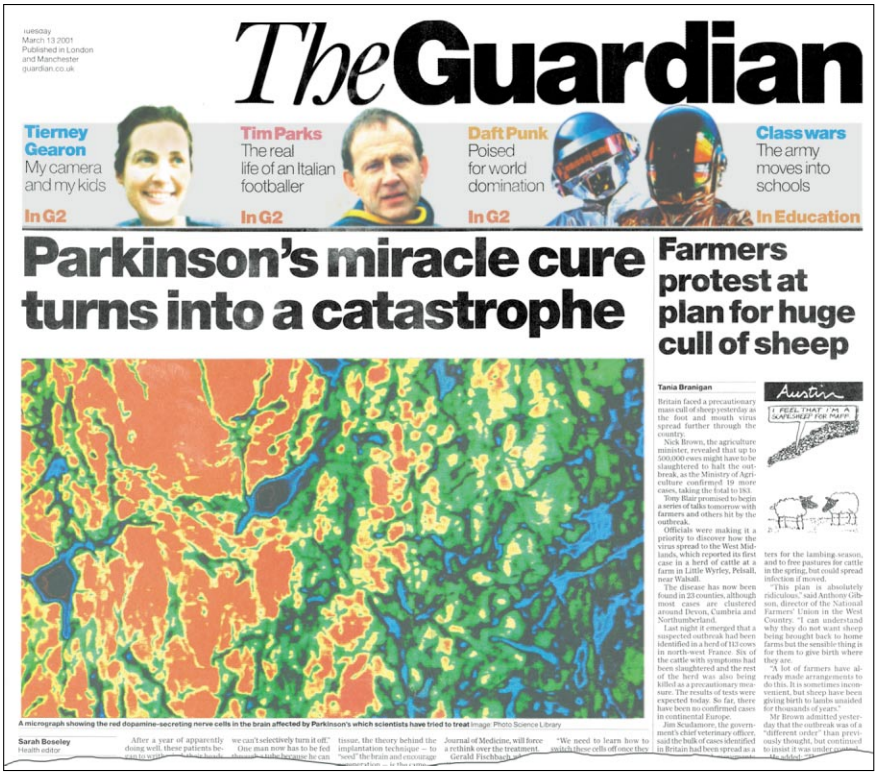
Gerald Fischbach, who was director of the National Institute of Neurological Disorders and Stroke, which sponsored the new study published in *The New England Journal of Medicine*, said that while the transplantation of foetal cells had been promoted by some neurosurgeons as miraculous, this was the first time it was rigorously evaluated. It used sham surgery as a comparison, a controversial and rarely used strategy but one the researchers felt was necessary to understand the true effects of the treatment.

In the study, researchers, led by Curt Freed of the University of Colorado Health Sciences Center in Denver and Stanley Fahn of the Columbia University College of Physicians and Surgeons, recruited 40 patients between the age of 34 and 75 who had had Parkinson's disease for an average of 14 years. The patients were randomly assigned to have substantia nigra cells from four foetuses implanted in their brains or to have sham surgery, for comparison.

The surgery took place in Colorado and the patients were evaluated in New York. The fetal cell surgery involved drilling four small holes in the patient's forehead and then inserting long needles through the holes into the brain. The sham surgery involved drilling the holes but not injecting needles into the brain.

The study's primary measure of success was whether the patients themselves noticed that they were better, as determined by a survey that they mailed in a year later but before they knew whether they had had foetal cell implants or a sham operation. The study found no difference between the two groups.

Parkinson's disease occurs when cells of the substantia nigra region in the base of the brain die, for unknown reasons. The hope is that fetal substantia nigra cells might take over for them. Most researchers welcomed the team's effort to carry out a controlled trial to build on the experimental work that has been



Headline gloom: The results of the first controlled trial of foetal graft treatment led to some critical media reports and concerns amongst researchers.

carried out over the past decade at several centres. Although many individuals have undergone treatment, without a controlled study the effects cannot be evaluated. Many researchers were concerned about the methods used by the team. "We wrote to *Science* in 1994 with some of our worries when the team published their planned protocol," says Marc Peschanski, a neuroscientist at Inserm in Paris.

Everyone agrees that foetal tissue is difficult to work with but many European researchers were concerned the the US team cultured the foetal cells before transplantation which may have reduced the number of viable cells present in the graft. There were also concerns about the surgery used which was different to most other groups and may have led to the graft not reinnervating the most interesting region, says Peschanski. Many researchers are now planning to write to the *NEJM* with their concerns.

Interest in the difficult foetal transplant approach to therapy was sparked by work by one of the pioneers of neurotransplantation, Anders Bjorklund at the University of Lund. He and his colleagues in 1975 were able to show in rats that foetal neurons transplanted to an adult brain could integrate and form new connections. This meant that the brain was capable of regeneration, which was a startling conclusion and contrary to what was believed at the time.

In 1985 his team first considered the possibility of transplants to patients suffering from Parkinson's disease. It took two years to consider the ethical implications and the first operation was not carried out until 1987 but by the end of last year 11 patients had been operated on at Lund with very encouraging results. Some have even been able to come off medication. "The Lund team are some of the best neurotransplanters," says neurobiologist George Foster at the University of Wales in Cardiff. "But without a controlled trial, the results officially count for nothing."

One drawback is the difficulty of practising such treatment on a large scale. It takes six foetuses, obtained from abortions, to acquire enough cells for a single patient, and it is therefore essential to find other sources of cell material for grafting. "The treatment requires such a wide range of highly specialised skills that it is only likely to be possible in large research centres," says Peschanski. Researchers in Europe and elsewhere are currently exploring a number of avenues. A group headed by Hakan Widner at the Wallenberg Neuroscience Centre in Lund has studied the possibility of grafting pig neurons and developed ways of preventing their rejection by the human immune system. Another key line of research is focusing on stem cells. Some researchers are also studying those which apparently exist in the brain. A network of researchers coordinated by Urban Lendahl at the Karolinska Institute, has identified neuronal stem cells in adult mice which can be a source of renewed neuron development.

But one of the key concerns for researchers seeking a real future for cell transplantation research is a means of turning off or destroying any transplanted cells producing unwanted products. Production of excess dopamine may have been responsible for the worst side effects in some of the patients in the US trial. "There should be a means of removing these cells if something goes wrong," says Foster. "Nicotine patches would never have won approval if you couldn't take them off," he says.